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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/725,013	12/02/2003	Lakshman R. Sehgal	3840-005-27	3180

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EXAMINER	
WHITEMAN, BRIAN A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 02/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/725,013	SEHGAL ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *14-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,28-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/1/04,6/25/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Non-Final Rejection

Claims 1-32 are pending.

The addition of claims 29-32 filed on 1/17/06 is acknowledged by the examiner.

The paper filed on 1/17/06 lists the claims readable on the elected species.

Election/Restrictions

Applicant's election with traverse of Group I (claims 1-13) and species unmodified hemoglobin and L-glutamine in the reply filed on 11/30/05 and 1/17/06 is acknowledged. The traversal is on the ground(s) that it would not be an undue burden on the examiner. This is not found persuasive because of the reasons set forth in the election restriction mailed on 11/30/05. The applicant has not address these reasons. However, the species (chemically modified hemoglobin) will be rejoined with the elected species (unmodified hemoglobin) because they are obvious variants of one another and both species will be examined with the elected invention.

The requirement is still deemed proper and is therefore made FINAL.

Claims 14-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Perfluorochemical emulsion in claim 10 and sodium bicarbonate and antibiotic-antimycotic in claims 12 and 28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11/30/05.

Specification

The use of the trademark pAdEasy, GIBCO, and STRATAGENE has been noted in this application. See pages 24 and 25. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Claim Objections

Claims 30-32 are objected to because of the following informalities:

A series of singular dependent claims is permissible in which a dependent claim refers to a preceding claim which, in turn, refers to another preceding claim.

A claim, which depends from a dependent claim, should not be separated by any claim, which does not also depend from said dependent claim. It should be kept in mind that a dependent claim may refer to any preceding independent claim. In general, applicant's sequence will not be changed. See MPEP § 608.01(n).

If claims 30-32 are allowed they will have to be renumbered to comply with MPEP 608.01(n).

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or

more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention, which is also disclosed, in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/430,099, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application.

Instant claims 2, 4, 5, 6, 7, and 8 do not have written support in application '099.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 6-13, and 28-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using a nucleic acid encoding a thrombomodulin protein or its variant, wherein the nucleic acid is operably linked to a promoter, does not reasonably provide enablement for using a nucleic acid not operably linked to a promoter. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claimed invention is a gutless adenovirus vector, which expresses a thrombomodulin protein comprising a polynucleotide encoding a thrombomodulin protein or its variant. The invention lies in the field of producing recombinant adenoviral vectors for use in ex vivo gene therapy.

Furthermore, with respect to claims 1, 2, 6-13, 28-32, the claims encompass a recombinant adenoviral vector, which expresses a thrombomodulin protein comprising a promoter not operatively to a specific nucleotide sequence. Claims 3-5 recite using a regulatory sequence operably linked to the polynucleotide sequence. Claims 1, 2, 6-13 and 28-32 are broader than the limitation in claims 3-5. The specification provides sufficient guidance for one skilled in the art to make and use a recombinant adenovirus vector, which expresses a protein comprising (a) promoter operatively linked to a polynucleotide sequence encoding a protein. However, the specification fails to provide sufficient guidance or evidence for one skilled in the art to make and use a recombinant adenoviral vector, which express a protein comprising a promoter that is not operatively linked to any specific nucleotide sequence in the adenoviral vector. The teachings in the specification are directed to using a regulatory element to express the protein. The specification provides guidance or evidence for how to make and use adenoviral vectors comprising a promoter operatively linked to polynucleotide to direct protein expression, however the claims do not recite such a structural limitation. Thus, to the extent the claims fail to recite distinguishing features to commensurate with the level of guidance presented, the claims are not considered enabled.

In conclusion, the specification and claims coupled with the state of the art at the time the invention was made provide enablement for using a polynucleotide operatively linked to a regulatory element. However, the rest of the disclosure encompassing a gutless adenoviral vector comprising a promoter not operatively linked to a nucleotide sequence from the adenoviral vector is not considered enabled. Given that making a recombinant adenoviral vector which expresses a desired protein comprising a promoter not operatively linked to the nucleotide sequence in the adenoviral vector was unpredictable at the time the invention was made, and given the lack of sufficient guidance for producing the claimed adenoviral vector, one skilled in the art would have to engage in a large quantity of undue experimentation in order to practice the full scope of the claimed invention based on the applicant's disclosure.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 3 and 4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3 and 4 recite the limitation "the DNA sequence". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 4, and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over French et al. (US 6,290,949) taken with Kochanek et al. (US 5981225). French teaches an ex vivo method of gene therapy for treating a vascular disease in a mammal (preferably human), comprising treating a graft (veins or arteries) with a gene transfer vector (replication defective adenoviral vector) comprising a nucleic acid operably linked to a promoter. See columns 13-18. The nucleic acid can encode TM. See column 5. French teaches that either the RSV promoter or

the CMV promoter can be used in the replication defective adenoviral vector. See column 7. However, French does not specifically teach using a gutless adenoviral vector in the method.

However, at the time the invention was made, one of ordinary skill in the art understood that gutless adenoviral vectors contain a minimal amount of adenovirus DNA and are incapable of expressing any adenovirus antigens. In addition, gutless adenovirus vectors provide significant advantage over first and second-generation adenoviral vectors because they can accommodate large inserts of foreign DNA while completely elimination the problem of expressing adenoviral genes that result in immunological response to viral proteins. See Kochanek et al. (columns 2-3). The instant specification teaches that, at the time of filing, several methods for producing gutless adenoviral vectors were known to one of ordinary skill in the art. See pages 17 and 24.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of French taken with Kochanek, namely to use a gutless adenoviral vector in the method. One of ordinary skill in the art would have been motivated to combine the teaching because gutless adenoviral vector eliminate the problem of expressing adenoviral genes that result in an immunological response to adenoviral proteins.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of French taken with Kochanek, namely to use the method to treat a human. One of ordinary skill in the art would have been motivated to combine the teaching to treat a human having a vascular disease because TM is well known to one of ordinary skill in the art for treating vascular disease in a subject.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Claims 1 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over French taken with Kochanek as applied to claims 1, 3, 4, and 8 above, and further in view of Salyapongse et al. (AL).

French taken with Kochanek do not specifically teach using an inducible system to control expression of the polynucleotide encoding TM.

However, at the time the invention was made, regulating transgene expression using inducible promoters was well known to one of ordinary skill in the art as exemplified by Salyapongse et al. (page 668). Salyapongse teaches that using an inducible promoter helps overcome the problem of controlling transgene expression using constitutive promoters (page 668).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of French taken with Kochanek in further view of Salyapongse, namely to use an inducible system to express the TM protein. One of ordinary skill in the art would have been motivated to combine the teaching because an inducible can be used to regulate the expression of the protein in the blood vessel.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Claims 1, 6, and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over French taken with Kochanek as applied to claims 1, 3, 4, and 8 above, and further in view of He et al. (PNAS, 95: 2509-2514).

French taken with Kochanek do not specifically teach using a shuttle vector with the structural limitations as recited instant claim 6 to produce the gutless adenoviral vector.

However, at the time the invention was made, the shuttle vector described in instant claim 6 was known to one of ordinary skill in the art as pAdEasy that can be ordered from Stratagene (page 24 of the instant specification). He et al. teaches that pAdEasy is a simplified system for generating adenoviruses (pages 2509-2510). He teaches that pAdEasy contains a kanamycin resistance gene (page 2510).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of French taken with Kochanek in further of He, namely to produce the gutless adenoviral using the claimed shuttle vector and use the gutless vector in the method. One of ordinary skill in the art would have been motivated to combine the teaching and use pAdEasy for producing the gutless adenoviral vector because pAdEasy is a simplified system for generating recombinant adenoviruses as exemplified by He (page 2509).

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Claims 1, 9-13, and 28-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over French taken with Kochanek as applied to claims 1, 3, 4, and 8 above, and further in view of Sehgal et al. (4,826,811) and Kibbe et al. (J. Vasc. Surg. 34: 156-65, 2001).

French taken with Kochanek do not specifically teach the method step recited in instant claims 9 and 28.

However, at the time the invention was made, an acellular oxygen carrier (unmodified hemoglobin or chemically modified hemoglobin) was well known to one of ordinary skill in the art for preserving a graft as exemplified by Sehgal et al. See column 4. In addition, the concentration for hemoglobin was well known to one of ordinary skill in the art as exemplified by Sehgal et al. See column 16.

In addition, at the time the invention was made, using a 1:1 mixture of Ham's F12 medium and DMEM for culturing a blood vessel (vein) in vitro transfected with a replication defective adenovirus was well known to one of ordinary skill in the art for as exemplified by Kibbe et al. See page 157. In addition, L-glutamine is used in the mixture. See page 157. Kibbe further teaches transfecting the vein with an E1 and E3 defective adenovirus and incubating the vein for 30 minutes. See page 157.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of French taken with Kochanek in further view of Sehgal and Kibbe, namely to the method steps as recited in instant claim 9, 28, and 29. One of ordinary skill in the art would have been motivated to combine the teaching because unmodified and chemically modified hemoglobin are used for preserving a graft. In addition, one of ordinary skill in the art would have been motivated to combine the teaching because a 1:1 mixture of Ham's F12 medium and DMEM was well known to one of ordinary skill in the art for culturing cells in vitro. Furthermore, one of ordinary skill in the art would have been motivated to incubate the blood vessel with the complex delivery system for a desired period of time (30

minutes) to assure sufficient transfection of the blood vessel with the gutless adenoviral viral vectors as exemplified by Kibbe (page 157).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of French taken with Kochanek in further view of Sehgal and, namely to the use unmodified hemoglobin in the range of 3 g/dl to 10 g/dl in the method. One of ordinary skill in the art would have been motivated to combine the teaching because the range was readily available to one of ordinary skill in the art for preserving a graft. See In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Double Patenting

Applicant is advised that should claim 12 be found allowable, claim 28 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Conclusion

Claims 1, 2, and 8 would be provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 24-26 and 28-29 of

copending Application No. 10/785,156. However, the claims of '156 are drawn to a non-elected invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, acting SPE – Art Unit 1635, can be reached at (571) 272-0811.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center number is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Brian Whiteman
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